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A Comprehensive Review on Solid lipid Nanoparticles for precision targeting in chemotherapeutic delivery

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ABSTRACT

To overcome the drawbacks of traditional drug delivery methods, solid lipid nanoparticles (SLNs) have become a ground-breaking platform for the precise targeting of chemotherapeutic drugs. For hydrophobic medications, SLNs—which are made of biocompatible solid lipids—offer a special blend of stability, regulated release, and improved bioavailability. Improved cellular uptake and the possibility of tailored delivery by surface modifications with ligands that identify particular cancer cell markers are made possible by their nanoscale size. SLNs are very beneficial in the treatment of cancer because of their focused approach, which reduces systemic toxicity and increases therapeutic efficacy. The ability of SLN formulation approaches to deliver chemotherapeutics has been further enhanced by recent developments, such as the addition of multifunctional targeting moieties and the optimization of lipid composition. Furthermore, SLNs can be designed to offer prolonged release profiles, which would improve patient compliance and lower the frequency of administration. The promise of solid lipid nanoparticles as a flexible and successful precision medicine approach in oncology is highlighted in this abstract, opening the door to safer and more efficient cancer treatments.

Keywords: *SLNs, chemotherapeutics, optimization, oncology.*

1. INTRODUCTION

Recently, there has been a lot of interest in colloidal delivery systems as possible drug delivery carriers. Solid lipid nanoparticles (SLN) are gaining a lot of interest as innovative colloidal drug carriers that offer an alternative to the current conventional carriers like emulsion, liposomes, and nanoparticles.[1] It is essential as a lipid matrix composed of physiological lipids that are free from the possibility of both acute and long-term harm. Because of the medication's physicochemical characteristics, which include limited permeability, short half-life, high molecular weight, and poor solubility, developing drug delivery carriers can be extremely difficult. To get beyond these obstacles, solid lipid nanoparticles (SLN) are a revolutionary drug delivery technology for pharmaceutical pharmaceuticals in a variety of application pathways. "Zero-dimensional" nanomaterials are another name for solid lipid nanoparticles. This definition results from the fact that all of their dimensions are in the nanoscale (under 100 nm), in contrast to two-dimensional nanomaterials (such as self-assembled monolayer films) and one-dimensional nanomaterials (such as nanowires and nanotubes), which have two dimensions larger than the nanoscale. Colloidal drug carrier systems are solid lipid nanoparticles (SLN).[2]

Due to their capacity to address the shortcomings of both microcapsules and nanoscalar colloidal carrier systems, solid lipid nanoparticles (SLN) have drawn more interest from the food and pharmaceutical industries.[1][2] They are the most recent generation of nanoscalar encapsulation systems, combining the benefits of parent liquid nanoemulsions or microemulsions

with high permeability of the active compound through the intestinal wall and high dissolution velocities. At the same time, they address issues related to the encapsulated compound's chemical and physical stability as well as handling ease.[3]

The solid core of SLNs is made up of physiologically acceptable and high-melting-point lipids, and the outside shell is covered in nontoxic amphiphilic surfactants. According to the barriers, nanoparticles entering and leaving the body should have the same submicron size range (50–1000 nm). The literature reveals that the physiochemical qualities and stability of drug-loaded SLNs rely on the drug's and its constituents' attributes. Particle size, long-term stability during storage, drug loading, and release behavior are all impacted by the proper selection of lipids, surfactants, and their composition. It indicates that by examining how process variables affect the properties of desired carriers, an ideal SLN formulation for any medication can be found.[4] The physicochemical characteristics of the drug substance, the type and concentration of surfactants, the kind of lipid and its crystallization pattern, and the production process that determines the drug substance distribution and incorporation efficiency of the SLN are some of the variables that affect the final SLN. To achieve effective encapsulation in the lipid, the medicinal ingredient is typically dissolved or distributed in the melted lipid phase prior to preparation by homogenization11. The drug substance's lipophilicity and solubility in the two phases most likely determine the incorporation efficiency.[5]

2. SOLID LIPID NANOPARTICLES (SLNS)

SLNs are sub-micron colloidal carriers made of physiological lipids that degrade naturally. Because of their biodegradable nature, SLNs are less harmful than polymeric nanoparticles. As an alternate system to the current conventional carriers including emulsion, liposomes, and nanoparticles, solid lipid nanoparticles (SLN) are garnering a lot of interest as innovative colloidal drug carriers.[5][6] It is essential because it is a lipid matrix composed of physiological lipids that are not susceptible to either acute or long-term damage. Drug delivery carrier development is frequently quite difficult. Triglycerides, complex glyceride combinations, or hard fat waxes are the lipids employed. Alternative nanoparticles constructed from solid lipids, or so-called solid lipid nanoparticles, have drawn the interest of many research groups since the mid-1990s.[7]

The SLN minimizes the drawbacks of existing cutting-edge carrier systems while combining their benefits (such as physical stability, regulated release, protection of integrated labile medicines against degradation, and great tolerability). SLN formulations have been created and extensively described both in vitro and in vivo for a variety of administration routes, including parenteral, oral, cutaneous, ophthalmic, pulmonary, and rectal. Recently, Nanobase, Yamanouchi, a topically applied moisturizer, was released onto the Polish market. Modifications of SLN, known as nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC) nanoparticles were introduced at the turn of the millennium. Figure 1 illustrates the structure of Solid lipid Nanoparticle (SLN)[8]

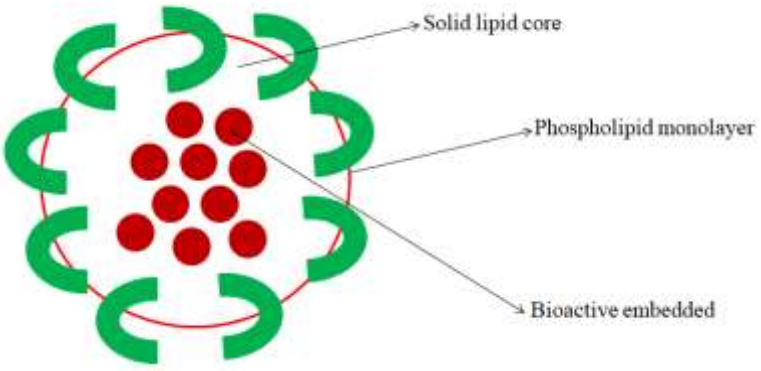

Figure 1: Structure of Solid Lipid Nanoparticle (SLN)

Advantages of Solid Lipid Nanoparticles (SLNs):[1]

- Utilizing biodegradable physiological lipids reduces the risk of acute and long-term toxicity and prevents the use of organic solvents during manufacture.
- Improved bioavailability of poorly water-soluble compounds.
- Site-specific medication administration, improved drug absorption by dermal application.
- Possibility of scaling up.
- Protection of sensitive molecules from the environment and of chemically labile substances against degradation in the gut.

- SLNs have better stability compared to liposomes.
- Increase the chemical synthesis of the labile integrated compound and bioavailability of the bioactives that have been captured.
- Lyophilization possible.

SLN's intrinsic low integration rate because of the solid's crystalline structure, particle growth, unpredictable gelation propensity, and unanticipated dynamics of polymorphic transitions are common drawbacks.[9]

3. METHODS OF PREPARATION

1. **High shear homogenization (HSH):** This technique is dependable and was first applied to the creation of solid lipid nanoemulsions. High pressure homogenization is used, which forces the liquid at high pressure (100–2000 bar) via a tiny opening that is only a few microns across. When the fluid's viscosity is exceeds 1000 km/h, it accelerates to a very small distance. The particles are disrupted down to the submicron level by extremely high shear stress and cavitation forces. Research has been done on lipid contents ranging from 5% to 40%. Hot and cold homogenizations are the two basic methods used to attain HSH. Typically, hot homogenization is done at temperatures higher than the lipid's melting point. A high shear mixing mechanism creates a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (at the same temperature).[10] The end outcome is a hot o/w emulsion, and as this emulsion cools, the lipid crystallizes and SLNs are formed. Higher processing temperatures result in smaller particle sizes due to the lipid phase's decreased viscosity. On the other hand, high temperatures accelerate the rate at which the medicine and carrier degrade. Because the particles have a high kinetic energy, increasing the homogenization temperature or the number of cycles frequently causes the particle size to rise. Typically, three to five homogenization cycles are employed at 500–1500 bar of pressure.[10][11]

To overcome the issues with temperature-related degradation, drug loss into the aqueous phase, and partitioning that come with the hot homogenization process, cold homogenization was created. The complexity of the nanoemulsion's crystallization phase causes unpredictable polymeric transitions of the lipid, leading to several modifications and/or super cooled melts. Here, the medication is mixed with melted lipid, which is then quickly cooled with liquid nitrogen or dry ice. A mortar mill grinds the solid material. Then, at room temperature or lower, the produced lipid microparticles are dispersed in a cold emulsifier solution. Effective temperature control is necessary to guarantee that the lipid remains solid during homogenization. But in contrast to greater particle sizes, heated homogenization, and a Cold homogenization samples typically have a wider size distribution.[12]

2. **Ultrasonication:** Another technique for creating SLNs is high-speed homogenization, often known as Ultrasonication. This approach has the benefit of using widely accessible lab-scale equipment. Nevertheless, this approach has drawbacks such a wider size dispersion that reaches into the micrometer range. Other issues with this method include possible metal contaminations and physical instability, such as particle development during storage.[13] Table 1 indicates a list of medications and polymers used in various techniques to prepare SLNs.

Table 1: List of medications and polymers used in various techniques to prepare SLNs[14]

Drug	Polymer	Method of preparation
Olanzapine	Hydrogenated soyaphosphatydylcholine	Modified high pressure homogenization
Rizatriptan	Tristearin,Phospholipon80	Modified solvent injection method
Alendronate NP	PLGA, Ethyl acetate, PF68	Double emulsion solvent diffusion
Clozapine Tetracaine, Etomidate, Prednisolone	Dynasan114,116, Tristearin,Dynasan112, Campritol 888ATO, Lipoid S75	Hot homogenization
Vitamin A Retinol	Compritol 888ATO, Miglyol 812, Dynasan 116	Hot homogenization
Gatifloxacin	Chitosan-Na aliginate	Modified Coacervation
Insulin	PEG'Glycolgrafted chitosan	Ionic gelation
Paclitaxel	Tripalmitin, phosphatidylcholine	Microemulsion

Insulin	Hydrophobized cholesterol bearing pullulan	Ultra sonication
Mitoxantrone	Glyceryl behenate, Campritol 888ATO, lecithin	Ultra sonication
Vinpocetine	Glyceryl monostearate, DCM, soyalecithin	Ultrasonic solvent emulsification
Insulin	Cetyl palmitate	Solvent emulsification evaporation
5-Fluorouracil	Dynasan 114,118, triglyceride, soyalecithin	Double emulsion Solvent evaporation
Methotrexate	Cetyl alcohol, Campritol 888 ATO, Tween 80	Microemulsion congealing technique
Gatifloxacin	Sodium alginate, Chitosan	Modified Coacervation

3. **SLN preparation using microemulsions:** Gasco and colleagues (1997) created SLNs based on the dilution of microemulsions, which are made by stirring an optically transparent mixture at 65–70°C. The mixture is usually made up of water, co-emulsifiers (such as butanol and sodium monooctylphosphate), an emulsifier (such as polysorbate 20 or polysorbate 60, soyaphosphatydylcholine and taurodeoxycholic acid sodium salt), and a low melting fatty acid like stearic acid. The hot microemulsion is dissolved in cold water (2–3°C) while being stirred, with typical volume ratios of the hot microemulsion to cold water in the range of 1:25 to 1:50.[15] The dilution process is crucially influenced by the microemulsion. The SLN dispersion can be utilized as granulation fluid for transferring in to solid product like tablets and pellets by granulation process, but in case of low particle content too much of water need to be removed. The nanoparticles were created only with solvents which disperse extremely swiftly into the aqueous phase (acetone), while bigger particle sizes were obtained with more lipophilic solvents.[16]

4. **Supercritical Fluid technology:** Recently, this innovative method has been used to produce SLNs. When a fluid's temperature and pressure both beyond its respective critical values, it is said to be supercritical. The fluid's capacity to dissolve substances improves. This technique includes a number of methods for producing nanoparticles, including supercritical fluid extraction of emulsions (SFEE), particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), and rapid expansion of supercritical solution (RESS).[17] This method's benefits include avoiding the use of solvents, producing particles as a dry powder rather than suspensions, and requiring only modest pressure and temperature. The best solvent option for this procedure is carbon dioxide solution.

5. **Solvent evaporation method:** The lipophilic substance is dissolved in cyclohexane, a water-immiscible organic solvent that is emulsified in an aqueous phase, in order to produce nanoparticle dispersions by precipitation in o/w emulsions. When the solvent evaporates, the lipid precipitates in the aqueous media, forming a dispersion of nanoparticles.[18] Using lecithin/sodium glycocholate combination as an emulsifier and cholesterol acetate as a model medication, the average diameter of the resulting particles was 25 nm. The Siekmann and Westesen (1996), who created cholesterol acetate nanoparticles with an average size of 29 nm, verified the reproducibility of the outcome.[19]

6. **Solvent emulsification-diffusion:** Another method for creating SLNs is the solvent emulsification-diffusion approach. The average particle size depending on the emulsifier employed and the amount of lipid in the organic phase. This method can produce particles with average sizes between 30 and 100 nm. The main benefit of this method is that heat is avoided during preparation. In this case, the lipid matrix is emulsified in an aqueous phase after being dissolved in a water-immiscible organic solvent. The lipid precipitates in the aqueous media, causing the solvent to evaporate at lower pressure and produce a dispersion of nanoparticles.[20]

7. **Double Emulsion:** This technique involves encapsulating the medication with a stabilizer to stop it from partitioning to the external aqueous phase as the solvent evaporates in the external w/o/w double emulsion water phase. Li et al. (2010) used the double emulsion approach to create solid lipid nanoparticles filled with bovine serum albumin (BSA).[21]

8. **Spray Drying:** It is a different method from lyophilization for turning an aqueous SLN dispersion into a pharmaceutical product. This approach is less expensive than lyophilization and suggests using lipids with a melting point higher than 70°C. Because of the high temperature shear pressures and partial melting of the particles, this process leads to particle aggregation. SLN concentrations of 1% in a trehalose in water solution or 20% in ethanol-water mixes (10/90 v/v) produced the greatest results, according to Freitas and Mullera (1998).[22]

9. **Solvent injection technique:** Here, a water-miscible solvent dissolves the solid lipid. With or without surfactant, the lipid

solvent mixture is injected into the agitated aqueous phase. The dispersion was then filtered to get rid of extra fat. According to Schubert et al. (2003), emulsion in the aqueous phase stabilizes SLNs until solvent diffusion is finished and helps to form lipid droplets at the injection site. In order to deliver the Hepatitis B surface antigen for immunization via the subcutaneous route, Mishra et al. (2010) produced and assessed SLNs utilizing the solvent injection approach.[23] Figure 2 describes Hot Homogenization & Cold Homogenization technique for the preparation of Solid Lipid Nanoparticles (SLNs)

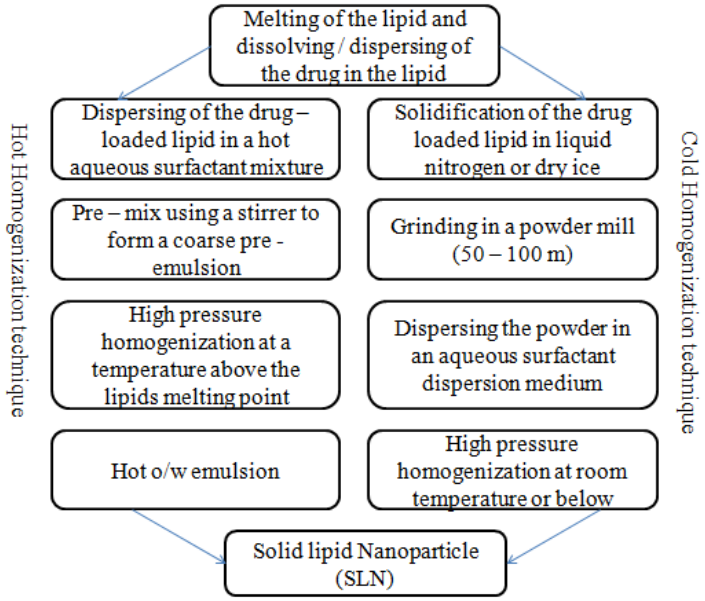

Figure 2: Hot Homogenization & Cold Homogenization technique for preparation of SLN

4. CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

1. **Particle size and Zeta potential:** The particle size of SLNs determines their physical stability. The most effective methods for determining particle size are laser diffraction (LD) and photon correlation spectroscopy (PCS). PCS, often referred to as dynamic light scattering, monitors how particle mobility causes the intensity of the scattered light to fluctuate. The size range of particles detected by photon correlation spectroscopy (PCS) is 3 nm to 3 µm, while the size range detected by laser diffraction is 100 nm to 180 µm. Despite being an effective tool for characterizing nanoparticles, PCS may also identify bigger microparticles.[24] A zeta potential analyzer or zeta meter can be used to measure zeta potential. To determine size and quantify zeta potential, SLN dispersions are diluted 50 times with the original dispersion preparation media before to measurement. Without additional complicating elements like steric stabilizers or hydrophilic surface appendages, a higher zeta potential value may cause the particles to deaggregate. Predictions regarding the storage stability of colloidal dispersions are made possible by zeta potential measurements.[25]

2. **Electron microscopy:** Nanoparticles can be directly observed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). However, SEM is superior for morphological analysis. The detection limit of TEM is modest.[25]

3. **Atomic force microscopy or AFM:** This method creates a topological map by rastering a probe tip with atomic scale sharpness across a sample, taking into account the forces acting between the tip and the surface. The precise type of force used helps to differentiate between the various sub-techniques.[26] The probe can be dragged across the sample (contact mode) or left hovering slightly above (non contact mode). This method allows for ultra-high resolution, which, when combined with the capability of mapping a sample based on characteristics other than size, such as colloidal attraction or resistance to deformation, makes AFM a useful tool.[27]

4. **Dynamic light scattering or DLS:** Quasi-elastic light scattering (QELS), commonly referred to as PCS or DLS, measures changes in scattered light intensity on a microsecond timescale. An autocorrelation function is compiled to quantify this variance, which is caused by the interference of light scattered by individual particles under the effect of Brownian motion. The method's advantages include its sensitivity to sub micrometer particles, rapidity of examination, and lack of calibration requirements.[28][29][30]

5. **Fraunhofer diffraction or Static light scattering:** With this approach, the pattern of light dispersed from a particle solution is gathered and fitted to basic electromagnetic equations where size is the main variable. Although it is a quick and reliable procedure, it necessitates more purity than DLS and advanced understanding of the optical properties of the

particles.[31]

6. **Differential scanning calorimetry or DSC:** The degree of crystallinity of the particle dispersion is ascertained by DSC and powder X-ray diffractometry (PXRD). By comparing the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion, the rate of crystallinity using DSC is determined.[32]

7. **Nuclear magnetic resonance or NMR Spectroscopy:** Nanoparticles' size and qualitative makeup can both be ascertained via NMR. In order to offer information on the physicochemical status of the components within the nanoparticle, the selectivity provided by chemical shift enhances the sensitivity to molecular mobility.[33]

8. **Acoustic methods:** Acoustic spectroscopy is another ensemble method that uses the fitting of physically relevant equations to detect the attenuation of sound waves in order to determine size. Furthermore, surface charge can be determined by detecting the oscillating electric field produced by charged particles moving under the effect of acoustic energy.[34]

5. ROLE OF SOLID LIPID NANOPARTICLES FOR PRECISION TARGETING IN CHEMOTHERAPEUTIC DELIVERY

Over the past 20 years, a number of chemotherapeutic drugs have been encapsulated in SLN, and their effectiveness has been assessed both in vitro and in vivo. An anticancer medication called tamoxifen has been added to SLN to extend the drug's release after intravenous treatment for breast cancer.[35] SLN loaded with medications such as camptothecin and methotrexate has been used to target tumors. Metoxantrone SLN local injections were developed to lessen the drug's toxicity and enhance its safety and bioefficacy in the treatment of lymph node metastases and breast cancer.

1. **Liver Cancer:** One of the most prevalent malignancies in the world is hepatocellular carcinoma (HCC), a primary malignancy of the liver. HCC has the second-highest cancer-related death rate in China during the 1990s, and its mortality rate is the third highest globally among all cancer-related disorders. The liver is the most typical organ for tumor metastases in addition to original malignancies. Stabilized lipid coated lipoplexes were proposed by Bartsch and colleagues (2004) for the delivery of antisense oligonucleotide (AS-ODN) to liver endothelial cells in vitro and in vivo.[36]

2. **Breast Cancer:** As the second highest cause of cancer-related fatalities in women, breast cancer is one of the most common malignancies in women. However, because to advancements in breast cancer therapy and prevention since 1989, the annual rate of breast cancer mortality has fallen by 1.8%. The development of resistance to several chemotherapeutic medicines, often known as multidrug resistance (MDR), is a significant clinical barrier in cancer therapy. Chemo resistance can often be caused by one of two things. First, by physically hindering delivery to the tumor (such as through inadequate absorption, excessive metabolism/excretion, and/or inadequate drug diffusion into the tumor mass); second, via intracellular processes that raise the threshold for cell death.[37] It is well known that nanoparticles are effective tumor targeting agents because of their enhanced permeability and retention (EPR) effect, which allows them to target tumors passively. As an added benefit, hiding the particles with a polyethylene glycol/oxide (PEG/PEO) surface modification prevents the reticulo endothelial system from absorbing them, extending their circulation time.[38]

3. **Colorectal Cancer:** The second biggest cause of cancer-related fatalities in the United States after lung cancer, colorectal cancer accounts for approximately 60,000 deaths annually in Western nations. For efficient delivery to colon cancers, oxaliplatin-bearing chitosan nanoparticles (L-OHP) encapsulated in Eudragit S100-coated pellets were produced. SLN have been proposed as a novel medicine delivery method. SLN including doxorubicin, paclitaxel, and cholesteryl butyrate had previously been created. Doxorubicin is less effective than it formerly was at treating colorectal cancer. SLN are in the colloidal size range and, depending on the technique of manufacture, can include both hydrophilic and lipophilic medicines.[39] Warm microemulsions can be made from a variety of ingredients, depending on the kind of medication and mode of administration.[40]

4. **Lung Cancer:** One of the biggest causes of mortality in the globe is lung cancer. The term "non-small cell lung cancers" (NSCLCs) refers to adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, which collectively account for the majority of lung malignancies. Surgery is frequently used to treat patients with early-stage NSCLC; depending on the stage of the cancer, 5-year survival rates range from 25% to 80%. Due to their inability to eradicate dispersed tumors with a tolerable degree of harm, current therapies for lung cancer have had little effectiveness.[41] Lung tumors are typically caused by mutations in the p53 gene, which can result in treatment resistance, increased tumor angiogenesis, cell proliferation, and suppression of apoptosis in addition to loss of tumor-suppressor activity. Gene therapy is a complementary approach that has demonstrated potential in the treatment of lung cancer. Viral and non-viral vectors are the two primary types of vectors used in gene delivery. Concerns about viral vectors immunogenicity and toxicity have stimulated research in non-viral techniques for gene delivery.[42] Biodegradable nanoparticles have demonstrated their superiority over other carriers among non-viral vectors by having greater stability and the capacity for regulated release. The two types of nanoparticles often used in gene delivery methods are cationic and anionic nanoparticles. In order to create stable polymer/lipids-DNA complexes, cationic nanoparticle systems take use of the ionic interaction between cationic polymers and anionic plasmid DNA. Solid lipid nanoparticle (SLN) systems and cationic lipid formulations have attracted more interest as attractive colloidal carrier systems. It has been shown that p53 gene/cationic lipid complexes can be used to treat early endobronchial carcinoma in place of viral

delivery methods.[43] Despite having less efficacy than viral vectors, cationic lipids may be advantageous when given over an extended period of time to several tumor sites spread across the bronchial epithelium. Additionally, the majority of potential non viral gene delivery methods exhibit zero immunogenicity.[44]

5. **Brain Tumor:** SLN is one of the best-characterized lipid-based nanoscale compounds created for the delivery of drugs to treat brain tumors. These nanoparticles are created via micro-emulsion or high-pressure homogenization of solid physiological lipids. Although the precise method by which SLNs penetrate the BBB and BTB is unknown, it is theorized that endocytosis of SLNs by endothelial cells serves as a mediator for internalization. The adsorption of circulating plasma proteins to the SLN surface is hypothesized to promote the process of endocytosis. Drugs may be loaded into SLN's lipid matrix while also being protected from degradation.[45] Depending on the SLN's surface coating and its component lipids, the drug unloading inside target tumor tissues may also be managed. The blood brain barrier was crossed by medicines, particularly when the polysorbate (Tween) surfactants were coated on the nanoparticles. The preoperative and intra operative identification of brain tumors may be revolutionized by SLN. About 43,800 primary brain tumors are diagnosed in the United States each year, according to estimates.[32] The use of nanodevices for the detection and treatment of brain cancers has rapidly expanded since the idea of applying nanotechnology to the imaging of gliomas was first out. There have been reports on a wide range of nanoparticle targeting possibilities, including peptides, cytokines, medications, antibodies, and ferromagnetic agents. Nanoparticles are quickly eliminated from the body when given systemically through the reticuloendothelial system. Opsonisation of nanoparticles, phagocytosis by macrophages, and uptake in the liver and spleen are all components of this process.[46] The binding of hydrophilic molecules to the surface of nanoparticles can partially prevent their clearance by the reticuloendothelial system. However, typical coating chemicals like polyethylene glycol and pluronic, which are used to produce a hydrophilic coating, might have immunogenic or inflammatory effects. The toxicity of nanoparticles (about 200 nm) on cerebral endothelial cells was used to infer that the BBB could be crossed, however another research that looked at comparable nanoparticles (about 300 nm) refuted this. Medication transport into the brain required a physical bond between the medication and the nanoparticles. Based on studies of manganese in various regions of the brain, it was also discovered that other SLN, such as manganese oxide, translocation to the brain via the olfactory pathway.[47]

6. **Gastro-intestinal Cancer:** The oral route is used to provide SLP medications for gastrointestinal malignancies. In the middle of the 1990s, SLN were launched as a new drug carrier technology for oral administration. According to reports, the adhesive qualities of nanoparticles boost bioavailability and lessen or eliminate irregular absorption. Nanoparticles can be absorbed through the mucosa of the gut by Peyer's patches, intracellular uptake, or the paracellular route, among other processes. Pinto and Muller (1999) examined the release of SLN for oral administration after incorporating it into spherical pellets. Granulates or powders of SLN can be added to pellets, crushed into tablets, or placed inside of capsules.[48] The transformation of the liquid dispersion into a dry product by spray-drying or lyophilization is helpful or frequently required for several of these applications. To determine if colloidal carriers are suitable for oral delivery, it is necessary to evaluate the stability of the carriers in GI fluids. First, their stability upon contact with GI fluids since they are composed of biodegradable materials and particle size in the nonorange maximizes the surface area for enzymatic degradation, and second, particle aggregation due to environmental conditions of the GI tract leading to decrease in the interaction capability of particles with the ion. These crucial factors have been largely ignored in the design of new and effective colloidal drug carrier systems for oral use.[49]

7. **Radionuclide nanoparticles for cancer treatment:** Injecting single doses of an atomic nanogenerator at kilobecquerel (nanocurie) levels into mice with solid prostate cancer or disseminated human lymphoma caused tumor regression and prolonged survival, without toxicity, in a significant portion of animals. Nanotechnology is also enabling highly effective chemotherapy.[50] When exposed to near infrared light, metal nanoshells with adjustable optical resonance were shown to cause irreversible thermal damage to tumor cells. Currently, the majority of targeted radionuclide therapy clinical studies use small molecules for both delivery and targeting, such as antibodies, shorter peptides, or radiolabeled biotin/avidin. Utilizing other carrier materials with larger radioactive doses and varied in-vivo behaviors, such as liposomes, dendrimers, and other structures with sizes on the order of several nanometers, may further enable advancement in the field of internal radionuclide treatment.[51]

8. **Overcoming Multidrug Resistance (MDR):** Despite the commercial development of numerous anticancer medicines for breast cancer, drug resistance continues to be a significant obstacle. Through a number of processes, MDR reduces the effectiveness of medications against cancer cells, which causes patients to not react to treatment. SLNs have several advantages over anticancer medications, such as reduced toxicity and enhanced drug stability. The MDR issue with some anti-breast cancer medications has just been resolved because to SLNs. For endocrine therapy of HR-positive breast cancer, particularly for ER-positive subtypes, tamoxifen is a well-established medication. As a selective estrogen receptor modulator that prevents the ER's transcriptional activity, tamoxifen belongs to the class of medications known as endocrine treatment.[52] Despite being in use for the past 40 years, tamoxifen resistance prevents about 50% of patients with ER-positive breast cancer from being cured. By modulating ER signaling, the ER antagonist tamoxifen produces its therapeutic benefits. Therefore, the loss of ER expression and function in cancer cells is the primary source of anti estrogen

resistance.[14] Furthermore, chemoresistance pathways in breast cancer involve the drug efflux transporter family known as the ATP-binding cassette (ABC) transporter family. Tamoxifen-resistant breast cancer cells express more ABC family proteins.[52] Through these mechanisms, breast cancer cells develop resistance to tamoxifen when it is administered over an extended period of time. The over expression of permeability glycoprotein (P-gp) due to abnormal ABC transporter family expression is one example of ABC family mechanism dysfunction. By triggering apoptosis, tamoxifen-SLNs counteract P-gp-mediated tamoxifen resistance. When treating breast cancer, the apoptotic action of SLNs may be able to overcome MDR.[53] Even in tamoxifen-resistant cells, tamoxifen-loaded SLNs can cause apoptosis and cell accumulation, reversing drug resistance developed during the G0/G1 phase. Anti-apoptotic gene expression was decreased by tamoxifen-SLN therapy, and miRNAs (miR-497 and miR-1280) were likewise suppressed. As a result, SLNs' apoptotic effect is a promising strategy for boosting medication effectiveness and reversing drug resistance in breast cancer (Figure 3).[32]

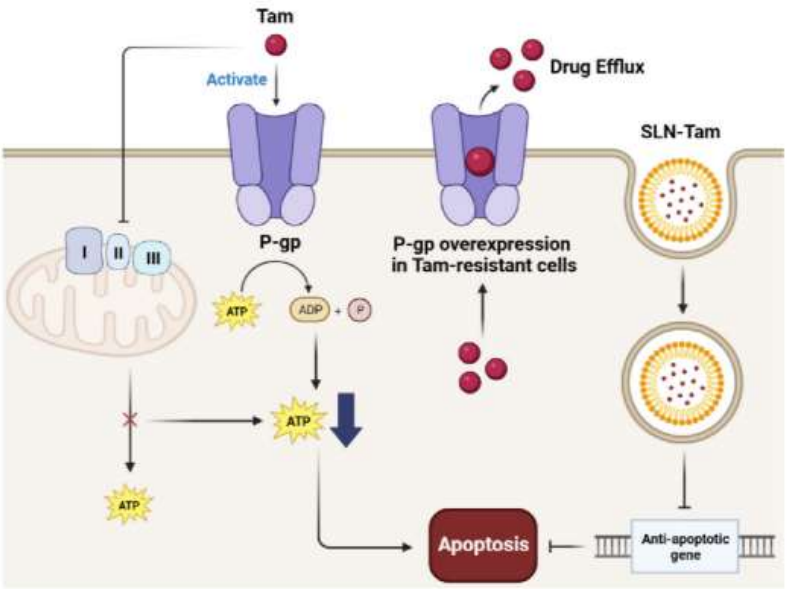

Figure 3: SLN-tamoxifen's function in cancer that is resistant to tamoxifen. By blocking complex I–III in the mitochondria and activating P-glycoprotein (P-gp), tamoxifen causes cancer cells to undergo apoptosis. ATP production is mediated by the mitochondrial electron transport complexes I–III. But another name for P-gp is a representative drug efflux transporter. Instead of increasing the anticancer effect, P-gp over expression in tamoxifen-resistant cancer cells increases drug efflux activity. By delivering medications straight to the cytosol and preventing the production of anti-apoptotic genes, SLN-tamoxifen overcomes resistance.[32]

9. **Magnetic nanoparticles for cancer treatment:** Research on magnetic nanoparticles (MNPs) for targeted medication administration and as the next-generation magnetic resonance imaging (MRI) contrast agents is ongoing. MNPs have undergone considerable testing as therapeutic tools for the targeted administration of medicines using magnetic drug targeting and active targeting including the attachment of high affinity ligands. Using a mouse xenograft model, Huh et al. (2005) recently revealed how superparamagnetic iron oxide (SPIO) nanoparticles may be utilized to detect cancer in-vivo. The nanoparticles in this study were coupled to the cancer-targeting antibody herceptin.[54] In order to find minor lymph node metastases in human prostate cancer patients, Harisinghani et al. (2003) used SPIO nanoparticles. For retention in the bloodstream and progressive absorption into the lymph nodes, where macrophages absorb them in this instance, the nanoparticles were coated with dextran. MNPs have undergone considerable testing as MRI contrast agents to enhance solid tumor detection, diagnosis, and treatment management. Currently, lesions as small as 2-3 mm may be distinguished by clinical imaging of liver cancers and metastases via reticulo-endothelium system-mediated absorption of SPIOs. The use of ultra superparamagnetic iron oxide MNPs to enhance the delineation of brain tumor borders and measure tumor sizes is another therapeutic application currently being studied.[55]

6. FUTURE ASPECTS

Due to the effective inclusion of active chemicals and the advantages associated with them, SLN make an appealing colloidal drug delivery method. An integrated strategy may be more effective than a reductionist one, despite the fact that most technologies have been centered on the delivery of specific chemotherapeutic drugs to tumors. By providing multimodal distribution with a single application, nanotechnology platforms can fill a special gap in this market. Although SLNs can be utilized for medication targeting, the drug must be released once it reaches the targeted sick spot in the body. Therefore, biodegradable nanoparticle formulations are required for medication delivery as the medicine must be transported and

released in order to be effective. It's interesting to note that while pharmaceutical scientists use nanoparticles to lessen the toxicity and side effects of pharmaceuticals, they were previously unaware that the carrier systems themselves may cause hazards to the patient. Nevertheless, we predict that more treatments and diagnostics based on nanotechnology will likely enter the clinic in the coming years.

7. CONCLUSION

The potential of solid lipid nanoparticles (SLNs) to improve the precise targeting of therapeutic drugs has made them a viable drug delivery technology, especially in the field of chemotherapy. Solid lipids, which make up SLNs, offer a stable matrix for encasing hydrophobic medications, enhancing their solubility and bioavailability. Because of their special qualities, which include their small size, biocompatibility, and adaptability for targeted distribution, SLNs can be used to get around the drawbacks of traditional chemotherapy. SLNs can bind to cancer cells selectively by functionalizing them with targeted ligands like peptides or antibodies. This minimizes systemic toxicity and off-target effects. Additionally, SLNs can help with regulated medication release, which lowers the frequency of delivery while enabling long-lasting therapeutic effects.

This focused strategy increases patient compliance and quality of life in addition to increasing the effectiveness of chemotherapeutic drugs. The effectiveness of SLNs in cancer treatment has been further enhanced by recent developments in their characterisation and formulation. To optimize the potential of SLNs in precision medicine, ongoing research is concentrated on investigating different lipid compositions, surface changes, and combination therapies.

All things considered, solid lipid nanoparticles are a flexible and efficient platform for the targeted administration of chemotherapeutic drugs, providing notable benefits in the treatment of cancer through increased therapeutic results, less side effects, and greater specificity.

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REFERENCES

[1] de Oliveira IF, Barbosa EJ, Peters MCC, Henostroza MAB, Yukuyama MN, dos Santos Neto E, et al. Cutting-edge advances in therapy for the posterior segment of the eye: Solid lipid nanoparticles and nanostructured lipid carriers. Int J Pharm 2020;589:119831. https://doi.org/10.1016/j.ijpharm.2020.119831.

[2] Carbone C, Fuochi V, Zielińska A, Musumeci T, Souto EB, Bonaccorso A, et al. Dual-drugs delivery in solid lipid nanoparticles for the treatment of Candida albicans mycosis. Colloids Surfaces B Biointerfaces 2020;186:110705. https://doi.org/10.1016/j.colsurfb.2019.110705.

[3] Tsilingiris D, Vallianou NG, Karampela I, Liu J, Dalamaga M. Potential implications of lipid nanoparticles in the pathogenesis of myocarditis associated with the use of mRNA vaccines against SARS-CoV-2. Metab Open 2022;13:100159. https://doi.org/10.1016/j.metop.2021.100159.

[4] Kiaie SH, Majidi Zolbanin N, Ahmadi A, Bagherifar R, Valizadeh H, Kashanchi F, et al. Recent advances in mRNA-LNP therapeutics: immunological and pharmacological aspects. J Nanobiotechnology 2022;20:1–20. https://doi.org/10.1186/s12951-022-01478-7.

[5] Kenjo E, Hozumi H, Makita Y, Iwabuchi KA, Fujimoto N, Matsumoto S, et al. Low immunogenicity of LNP allows repeated administrations of CRISPR-Cas9 mRNA into skeletal muscle in mice. Nat Commun 2021;12:1–13. https://doi.org/10.1038/s41467-021-26714-w.

[6] Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater 2021;6:1078–94. https://doi.org/10.1038/s41578-021-00358-0.

[7] Borges A, de Freitas V, Mateus N, Fernandes I, Oliveira J. Solid lipid nanoparticles as carriers of natural phenolic compounds. Antioxidants 2020;9:1–24. https://doi.org/10.3390/antiox9100998.

[8] Pandey S, Shaikh F, Gupta A, Tripathi P, Yadav JS. A Recent Update: Solid Lipid Nanoparticles for Effective Drug Delivery. Adv Pharm Bull 2022;12:17–33. https://doi.org/10.34172/apb.2022.007.

[9] Al-Najjar BY, Hussain SA. Solid lipid nanoparticles delivery systems for colon cancer chemotherapy: A critical review. Syst Rev Pharm 2020;11:1152–61. https://doi.org/10.31838/srp.2020.6.168.

[10] Carvalho PM, Felício MR, Santos NC, Gonçalves S, Domingues MM. Application of light scattering techniques to nanoparticle characterization and development. Front Chem 2018;6:1–17. https://doi.org/10.3389/fchem.2018.00237.

[11] Guevara ML, Persano F, Persano S. Advances in Lipid Nanoparticles for mRNA-Based Cancer Immunotherapy. Front Chem 2020;8:1–17. https://doi.org/10.3389/fchem.2020.589959.

[12] Kaeser GE, Chun J. Mosaic Somatic Gene Recombination as a Potentially Unifying Hypothesis for Alzheimer's

Disease. Front Genet 2020;11:1–11. https://doi.org/10.3389/fgene.2020.00390.

[13] El-Housiny S, Eldeen MAS, El-Attar YA, Salem HA, Attia D, Bendas ER, et al. Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: Formulation and clinical study. Drug Deliv 2018;25:78–90. https://doi.org/10.1080/10717544.2017.1413444.

[14] Garud A, Singh D, Garud N. Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. Int Curr Pharm J 2012;1:384–93. https://doi.org/10.3329/icpj.v1i11.12065.

[15] Scioli Montoto S, Muraca G, Ruiz ME. Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects. Front Mol Biosci 2020;7:1–24. https://doi.org/10.3389/fmolb.2020.587997.

[16] Bhagwat GS, Athawale RB, Gude RP, Md S, Alhakamy NA, Fahmy UA, et al. Formulation and Development of Transferrin Targeted Solid Lipid Nanoparticles for Breast Cancer Therapy. Front Pharmacol 2020;11:1–12. https://doi.org/10.3389/fphar.2020.614290.

[17] Chaudhuri A, Kumar DN, Shaik RA, Eid BG, Abdel-Naim AB, Md S, et al. Lipid-Based Nanoparticles as a Pivotal Delivery Approach in Triple Negative Breast Cancer (TNBC) Therapy. Int J Mol Sci 2022;23. https://doi.org/10.3390/ijms231710068.

[18] Ganesan P, Ramalingam P, Karthivashan G, Ko YT, Choi DK. Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases. Int J Nanomedicine 2018;13:1569–83. https://doi.org/10.2147/IJN.S155593.

[19] Liang Z, Zhang Z, Yang J, Lu P, Zhou T, Li J, et al. Assessment to the antifungal effects in vitro and the ocular pharmacokinetics of solid-lipid nanoparticle in rabbits. Int J Nanomedicine 2021;16:7847–57. https://doi.org/10.2147/IJN.S340068.

[20] Ghaderkhani J, Yousefimashouf R, Arabestani M, Roshanaei G, Asl SS, Abbasalipourkabir R. Improved antibacterial function of Rifampicin-loaded solid lipid nanoparticles on Brucella abortus. Artif Cells, Nanomedicine Biotechnol 2019;47:1181–93. https://doi.org/10.1080/21691401.2019.1593858.

[21] Yu Y, Cui X, Zhao J, Jia T, Ren B, Zhang X. Effect of Entecavir Combined with Adefovir Dipivoxil on Clinical Efficacy and TNF- α and IL-6 Levels in Patients with Hepatitis B Cirrhosis. J Oncol 2021;2021. https://doi.org/10.1155/2021/9162346.

[22] Gómez-Aguado I, Rodríguez-Castejón J, Vicente-Pascual M, Rodríguez-Gascón A, Pozo-Rodríguez A Del, Aspiazu MÁS. Nucleic Acid Delivery by Solid Lipid Nanoparticles Containing Switchable Lipids: Plasmid DNA vs. Messenger RNA. Molecules 2020;25. https://doi.org/10.3390/MOLECULES25245995.

[23] Langer R. Drug Delivery Systems. MRS Bull 1991;16:47–9. https://doi.org/10.1557/S0883769400056050.

[24] Pignatello R, Leonardi A, Fuochi V, Petronio GP, Greco AS, Furneri PM. A method for efficient loading of ciprofloxacin hydrochloride in cationic solid lipid nanoparticles: Formulation and microbiological evaluation. Nanomaterials 2018;8:1–11. https://doi.org/10.3390/nano8050304.

[25] Chirio D, Peira E, Dianzani C, Muntoni E, Gigliotti CL, Ferrara B, et al. Development of solid lipid nanoparticles by cold dilution of microemulsions: Curcumin loading, preliminary in vitro studies, and biodistribution. Nanomaterials 2019;9. https://doi.org/10.3390/nano9020230.

[26] Bayón-Cordero L, Alkorta I, Arana L. Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. Nanomaterials 2019;9. https://doi.org/10.3390/nano9030474.

[27] Arana L, Gallego L, Alkorta I. Incorporation of antibiotics into solid lipid nanoparticles: A promising approach to reduce antibiotic resistance emergence. Nanomaterials 2021;11. https://doi.org/10.3390/nano11051251.

[28] Tulbah AS, Lee WH. Physicochemical characteristics and in vitro toxicity/anti-sars-cov-2 activity of favipiravir solid lipid nanoparticles (Slns). Pharmaceuticals 2021;14. https://doi.org/10.3390/ph14101059.

[29] Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics 2018;10:1–17. https://doi.org/10.3390/pharmaceutics10020057.

[30] Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, et al. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics 2018;10:1–21. https://doi.org/10.3390/pharmaceutics10040191.

[31] Faria MJ, Lopes CM, Das Neves J, Lúcio M. Lipid nanocarriers for anti-HIV therapeutics: A focus on physicochemical properties and biotechnological advances. Pharmaceutics 2021;13. https://doi.org/10.3390/pharmaceutics13081294.

[32] Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of Solid Lipid Nanoparticles in Breast Cancer Therapy. Pharmaceutics 2023;15:1–14. https://doi.org/10.3390/pharmaceutics15082065.

[33] Danaei M, Kalantari M, Raji M, Samareh Fekri H, Saber R, Asnani GP, et al. Probing nanoliposomes using single particle analytical techniques: effect of excipients, solvents, phase transition and zeta potential. Heliyon 2018;4:e01088. https://doi.org/10.1016/j.heliyon.2018.e01088.

[34] Hosseini SM, Abbasalipourkabir R, Jalilian FA, Asl SS, Farmany A, Roshanaei G, et al. Doxycycline-encapsulated solid lipid nanoparticles as promising tool against Brucella melitensis enclosed in macrophage: A pharmacodynamics study on J774A.1 cell line. Antimicrob Resist Infect Control 2019;8:1–12. https://doi.org/10.1186/s13756-019-0504-8.

[35] Chenthamara D, Subramaniam S, Ramakrishnan SG, Krishnaswamy S, Essa MM, Lin FH, et al. Therapeutic efficacy of nanoparticles and routes of administration. Biomater Res 2019;23:1–29. https://doi.org/10.1186/s40824-019-0166-x.

[36] Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. Sci Rep 2021;11:1–11. https://doi.org/10.1038/s41598-021-90551-6.

[37] Zheng G, Zheng M, Yang B, Fu H, Li Y. Improving breast cancer therapy using doxorubicin loaded solid lipid nanoparticles: Synthesis of a novel arginine-glycine-aspartic tripeptide conjugated, pH sensitive lipid and evaluation of the nanomedicine in vitro and in vivo. Biomed Pharmacother 2019;116:109006. https://doi.org/10.1016/j.biopha.2019.109006.

[38] DeMichele A, Cristofanilli M, Brufsky A, Liu X, Mardekian J, McRoy L, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2− metastatic breast cancer in US real-world clinical practice. Breast Cancer Res 2021;23:1–10. https://doi.org/10.1186/s13058-021-01409-8.

[39] Dhiman N, Awasthi R, Sharma B, Kharkwal H, Kulkarni GT. Lipid Nanoparticles as Carriers for Bioactive Delivery. Front Chem 2021;9. https://doi.org/10.3389/fchem.2021.580118.

[40] Yan H, Luo B, Wu X, Guan F, Yu X, Zhao L, et al. Cisplatin induces pyroptosis via activation of meg3/nlrp3/caspase-1/gsdmd pathway in triple-negative breast cancer. Int J Biol Sci 2021;17:2606–21. https://doi.org/10.7150/ijbs.60292.

[41] Raut ID, Doijad RC, Mohite SK, Manjappa AS. Preparation and Characterization of Solid Lipid Nanoparticles Loaded with Cisplatin. J Drug Deliv Ther 2018;8:125–31. https://doi.org/10.22270/jddt.v8i6.2033.

[42] Wang W, Chen T, Xu H, Ren B, Cheng X, Qi R, et al. Curcumin-loaded solid lipid nanoparticles enhanced anticancer efficiency in breast cancer. Molecules 2018;23:1–13. https://doi.org/10.3390/molecules23071578.

[43] Paiva KLR, Radicchi MA, Báo SN. In Vitro Evaluation of NLS-DTX Activity in Triple-Negative Breast Cancer. Molecules 2022;27. https://doi.org/10.3390/molecules27154920.

[44] De A, Roychowdhury P, Bhuyan NR, Ko YT, Singh SK. Folic Acid Functionalized Diallyl Trisulfide – Solid Lipid 2023:1–17.

[45] Wang C, Zhang Y, Dong Y. Lipid Nanoparticle-mRNA Formulations for Therapeutic Applications. Acc Chem Res 2021;54:4283–93. https://doi.org/10.1021/acs.accounts.1c00550.

[46] Giordano A, Tommonaro G. Curcumin and cancer. Nutrients 2019;11. https://doi.org/10.3390/nu11102376.

[47] Lim M, Badruddoza AZM, Firdous J, Azad M, Mannan A, Al-Hilal TA, et al. Engineered nanodelivery systems to improve dna vaccine technologies. Pharmaceutics 2020;12:1–29. https://doi.org/10.3390/pharmaceutics12010030.

[48] Aldosari BN, Alfagih IM, Almurshedi AS. Lipid nanoparticles as delivery systems for RNA-based vaccines. Pharmaceutics 2021;13:1–29. https://doi.org/10.3390/pharmaceutics13020206.

[49] Karim ME, Haque ST, Al-Busaidi H, Bakhtiar A, Tha KK, Holl MMB, et al. Scope and challenges of nanoparticle-based mRNA delivery in cancer treatment. Arch Pharm Res 2022;45:865–93. https://doi.org/10.1007/s12272-022-01418-x.

[50] Mendes BB, Conniot J, Avital A, Yao D, Jiang X, Zhou X, et al. Nanodelivery of nucleic acids. Nat Rev Methods Prim 2022;2. https://doi.org/10.1038/s43586-022-00104-y.

[51] Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid Nanoparticles from Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS Nano 2021;15:16982–7015. https://doi.org/10.1021/acsnano.1c04996.

[52] Ahmad I, Pandit J, Sultana Y, Mishra AK, Hazari PP, Aqil M. Optimization by design of etoposide loaded solid lipid nanoparticles for ocular delivery: Characterization, pharmacokinetic and deposition study. Mater Sci Eng C 2019;100:959–70. https://doi.org/10.1016/j.msec.2019.03.060.

[53] Rupenganta A, Somasundaram I, Ravichandiram V, Kausalya J, Senthilnathan B. Solid lipid nanoaprticles- A

versatile carrier system. J Pharm Res 2011;4:2069–75.

[54] Ball RL, Bajaj P, Whitehead KA. Oral delivery of siRNA lipid nanoparticles: Fate in the GI tract. Sci Rep 2018;8:1–12. https://doi.org/10.1038/s41598-018-20632-6.

[55] Chaves LL, Lima S, Vieira ACC, Ferreira D, Sarmento B, Reis S. Overcoming clofazimine intrinsic toxicity: statistical modelling and characterization of solid lipid nanoparticles. J R Soc Interface 2018;15. https://doi.org/10.1098/rsif.2017.0932.